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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/468,145	06/06/95	ENGEL J	Y17506/93-11

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EXAMINER	
MINNIFIELD,N	
ART UNIT	**PAPER NUMBER**
1645	19

DATE MAILED: 11/17/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory Action

Application No.	Applicant(s)
08/468,145	ENGEL ET AL
Examiner	**Group Art Unit**
N. M. MINNIFELD	1645

THE PERIOD FOR RESPONSE: [check only a) or b)]

a) ☐ expires _____ months from the mailing date of the final rejection.

b) ☒ expires either three months from the mailing date of the final rejection, or on the mailing date of this Advisory Action, whichever is later. In no event, however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☐ Appellant's Brief is due two months from the date of the Notice of Appeal filed on _____ (or within any period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).

Applicant's response to the final rejection, filed on *Oct 20, 1998* **has been considered with the following effect, but is NOT deemed to place the application in condition for allowance:**

☒ The proposed amendment(s):

☒ will be entered upon filing of a Notice of Appeal and an Appeal Brief.

☐ will not be entered because:

☐ they raise new issues that would require further consideration and/or search. (See note below).

☐ they raise the issue of new matter. (See note below).

☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: _____

☐ Applicant's response has overcome the following rejection(s):

_____

☐ Newly proposed or amended claims _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claims.

☒ The affidavit, exhibit or request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See attached.

☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

☒ For purposes of Appeal, the status of the claims is as follows (see attached written explanation, if any):

Claims allowed: _____

Claims objected to: _____

Claims rejected: *12-23*

☐ The proposed drawing correction filed on _____ ☐has ☐has not been approved by the Examiner.

☐ Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s). _____ .

☒ Other *Interview Summary Record of 10-29-98.*

N. M. MINNIFELD
PRIMARY EXAMINER
ART UNIT 1645

ADVISORY ACTION

1. Applicants' request for reconsideration filed October 20, 1998 is acknowledged and has been entered. Claims 12-23 are now pending in the present application. All rejections have been withdrawn, in view of Applicants' amendment, with the exception of those discussed below.

2. Claims 12-19 and now 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Callahan et al, Finkenaur (EP 88-308573), Reissman et al and Moore, taken with Sauerbier et al. This rejection is maintained for the reasons set forth below.

Callahan et al teach "...removal of the HF under vacuum, the resin was washed with ether and air dried. The resin was then extracted with 10% HOAc (120 ml), 1% HOAc (120 ml) and water (120 ml). The aqueous extracts were combined, diluted with water and lyophilized to yield 213 mg crude linear peptide. 100 mg crude linear peptide was purified by gel filtration on G-15 with 1% HOAc to yield." (col 13, l. 8-14). The prior art teaches solubilization of heptapeptide in approximately 100-10,000 parts by weight of acetic acid for each part of peptide wherein the peptide is subsequently transferred to water followed by lyophilization. Finkenaur et al teach a method of lyophilizing a decapeptide in the presence of the bulking agent mannitol. Reissman et al discloses the use of cetrorelix in a pharmaceutical composition. Moore et al teach the conventional method of lyophilization; the lyophilizing peptides of 3-15 amino acids after solubilization in a sufficient amount of acetic acid to form a solution (cols. 7-8). The prior art teaches the claimed invention except for specifically reciting that the product was a sterile lyophilizates.

However, Sauerbier et al teach the lyophilization of a product for use and that this peptide had been sterilized (abstract; claims). Sauerbier et al teach "...sterile filtration of the solution only occurs immediately before filling into injection jars. This ensure greater microbiological safety than does the of sterile crystallizate." (col. 2). Sauerbier et al teaches that the prepared solution is sterilized by filtration using pathogen proof filters conventionally used for this purpose..." (col. 6, l. 41-43).

The claims are directed to a method of preparing a sterile lyophilizates of gel-forming peptide salts by dissolving peptide salts in acetic acid to form a solution, diluting the solution with water, adding a bulking agent, and sterile-filtering the solution, dispensing into vials and lyophilizing the solution.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to incorporate the method of Callahan et al, the addition of the bulking agent mannitol as taught by Finkenaur with the reasonable expectation of success of making a lyophilizate of cetrorelix as taught in Reissmann et al. The prior art teaches the concept of lyophilizing small peptides. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to sterile filter the peptide so that it would be in a sterile for administration to a human; solubilization of peptides after dissolution in acetic acid will result in stabilization of the peptide and therefore greater usefulness in pharmaceutical applications. The claimed invention is prima facie obvious in view of the prior art absent any convincing evidence to the contrary.

Applicant's arguments filed April 20, 1998 have been fully considered but they are not persuasive. Applicants have asserted that Finkenauer would not suggest to one skilled in the art

how to make a sterile lyophilisate of the decapeptide Cetrorelix; and that one can not compare a decapeptide with a polypeptide. Applicants have asserted that the prior art does not disclose a medically usable sterile lyophilized Cetrorelix or such a sterile peptide. The method as claimed can be used for any size peptide or polypeptide; it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the appropriate filter for sterile filtration of a peptide or polypeptide. It would have also been obvious to a person of ordinary skill in the art at the time the invention was made to sterile for the purpose of having a medicinal or pharmaceutical composition to be administered to a patient. Sauerbier et al discloses sterilization via filtration for safety purposes to avoid contamination (col. 2). It is noted that Applicants have argued against the references individually; however, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Applicant's arguments filed October 20, 1998 have been fully considered but they are not persuasive. Applicants' arguments have been previously addressed. Applicants have asserted that the person of ordinary skilled in the art would not be able to conclude from the cited art that by solubilizing a gel-forming peptide in acetic acid, a sterile filterable solution can be manufactured. Applicants have asserted that gel-forming properties of a peptide are caused by interaction between molecules. These properties depend very strongly on the chemical structure of the peptide and can't be reliably predicted. The properties also depend on concentration of solution and time allowed. However, Applicants have not shown that these are critical elements to the claimed novelty or unobviousness of the claimed invention. Applicants have not provided any evidence of unexpected results. Further, upon review of the specification, the recitation of "...method for preparation of sterile lyophilizates of gel-forming peptides..." does not appear to have support found on the specification. The original claims not recite "the gel-forming peptides" only "peptides which contain 3-15 amino acids". The specification discloses that the literature teach that oligopeptides with terminal acid amide function, tend to form gels. "During sterile filtration this is apparent from the speed of filtration, indeed the increased viscosity of such solutions can often already be detected organoleptically. A gelatinous layer remains on the sterile filter. It is then no longer possible to prepare a medication with an exactly and reproducibly defined active substance content." (p. 3, l. 8-20). There are no enabling statements or written descriptions of this "gel-forming peptide". The specification appears to suggests that it is too difficult to prepare such a gel-forming peptide and that it is not possible to prepare a medication with an exactly and reproducibly defined active substance content. The specification discloses that mannitol and other auxiliary substances were tested as filtration supporting agents to prevent

gel formation (p. 4, l. 22-28). These statements are not understood in view of the pending claim recitation.

3. No claims are allowed.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is (703) 305-3394. The examiner can normally be reached on Monday-Thursday from 7:00 AM-4:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D., can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

N. M. Minnifield

November 16, 1998

NITA MINNIFIELD
PRIMARY EXAMINER